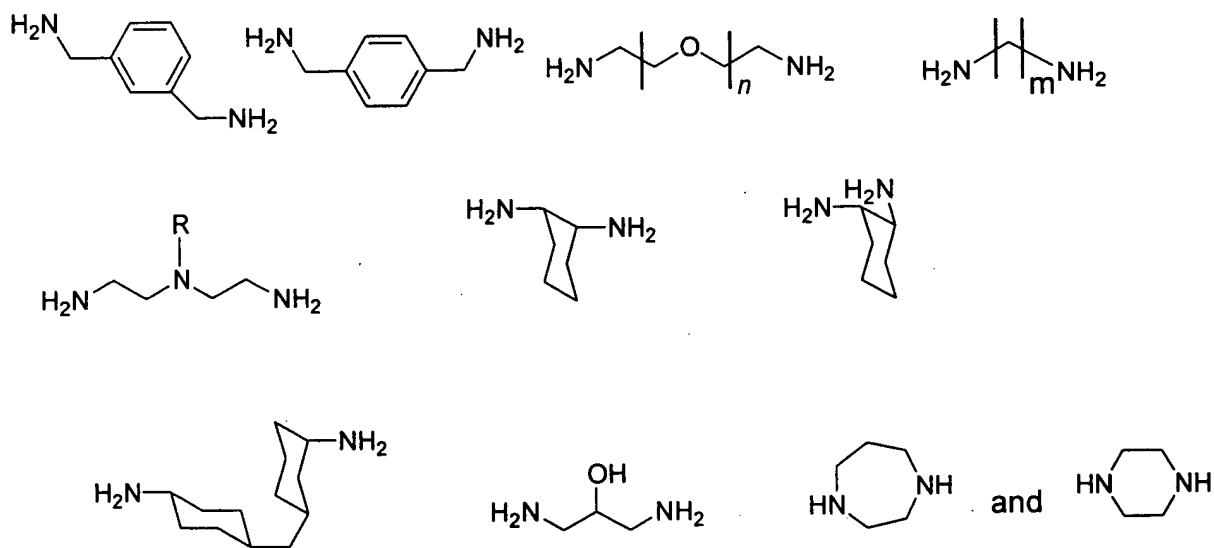


**WHAT IS CLAIMED IS:**

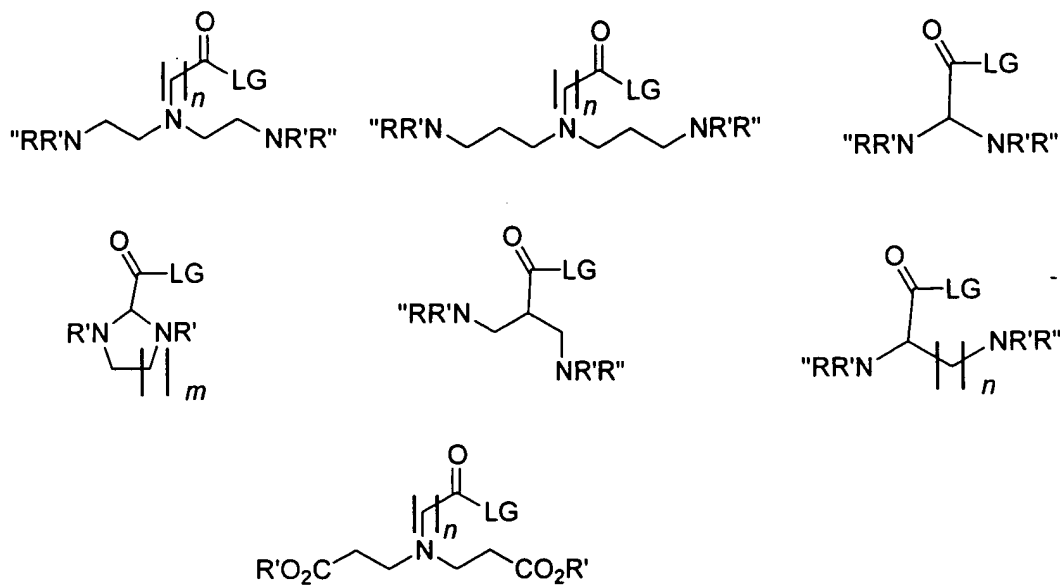
1. A method of making an MR imaging agent, said method comprising:
  - a) reacting a peptide having an N-terminal amine functional group with a linker-subunit moiety to form a modified peptide having a C-terminal amine functional group and said N-terminal amine functional group;
  - b) covalently attaching a linker moiety to the C-terminal amine functional group and to the N-terminal amine functional group to form a precursor MR imaging agent; and
  - c) converting the precursor MR imaging agent to the MR imaging agent.
2. The method of claim 1, wherein the linker-subunit moiety is selected from the group consisting of:



wherein:

- n is an integer from 1 to 4;
- m is an integer selected 1 to 12; and
- R is an aliphatic or aromatic group.

3. The method of claim 1, wherein the linker moiety is selected from the group consisting of



wherein:

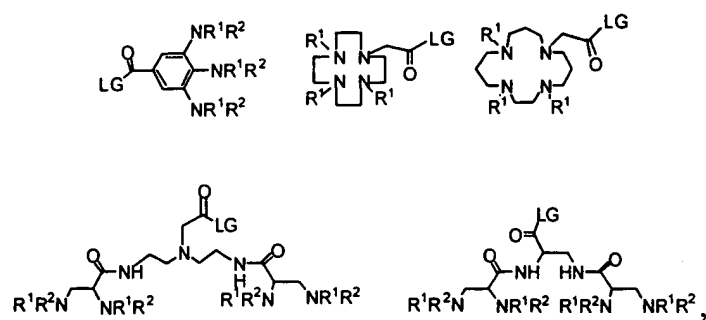
m is an integer from 1 to 4;

n is an integer from 0 to 4;

LG is a leaving group; and

R' and R'' independently are selected from the group consisting of hydrogen and a chemical protecting group.

4. The method according to claim 1, wherein the linker moiety is selected from the group consisting of:



wherein;

LG is a leaving group; and

R<sup>1</sup> and R<sup>2</sup> independently are selected from the group consisting of hydrogen and a chemical protecting group.

5. The method of claim 3 or claim 4, wherein the LG is selected from the group consisting of –OH, activated ester, halide, and anhydride, and wherein the chemical protecting group is selected from the group consisting of Boc, Fmoc, CBZ, t-butyl, benzyl, and allyl.

6. The method of claim 5, wherein the activated ester is selected from the group consisting of pentafluorophenol (Pfp), N-hydroxysuccinimide (NHS), N-Hydroxysulfosuccinimide Sodium Salt (NHSS), 2-Thioxothiazolidin-1-yl, and hydroxybenzotriazole (OBT).

7. The method of claim 5, wherein the halide is selected from the group consisting of F, Cl, Br, and I.

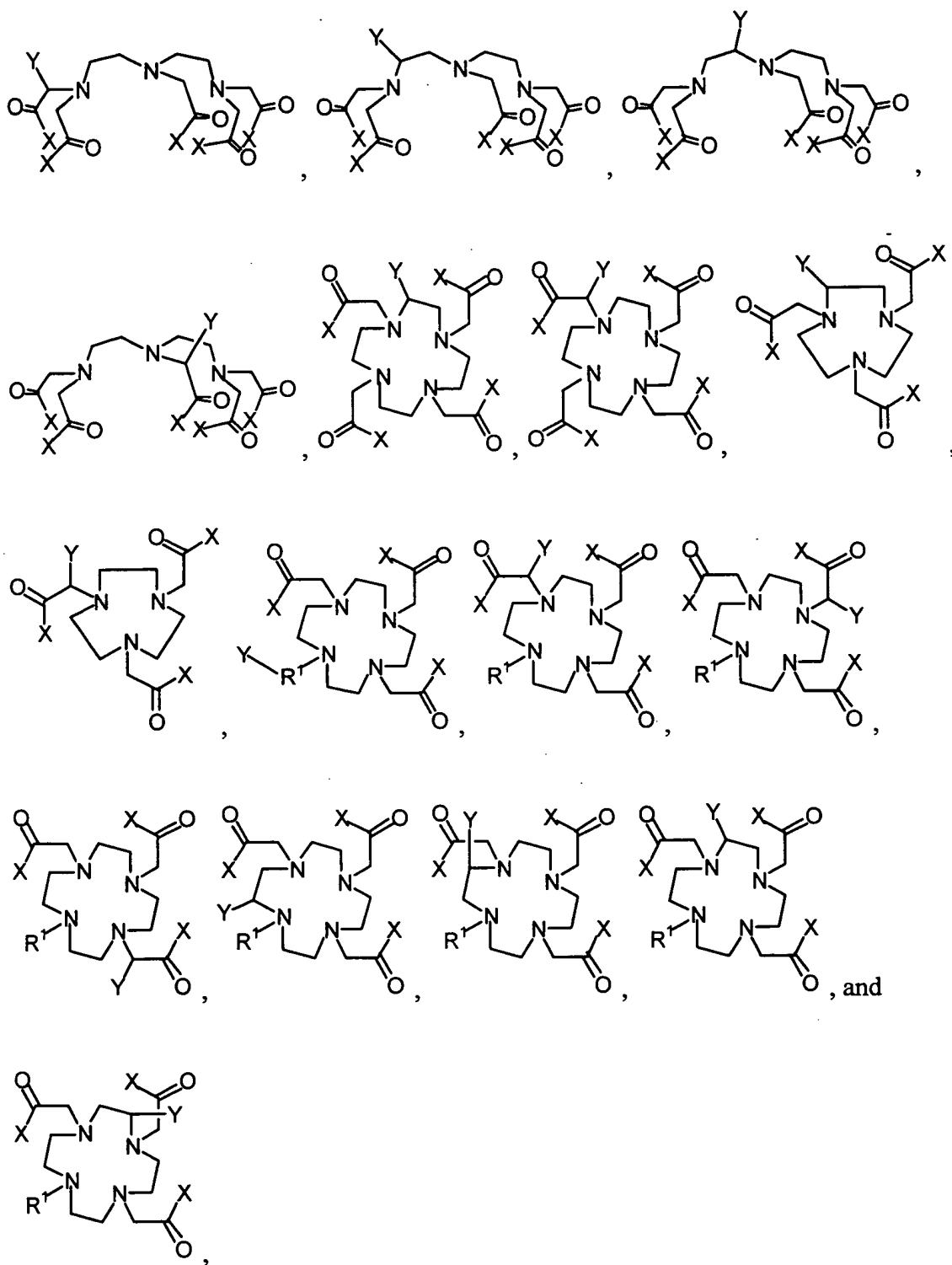
8. The method of claim 1, wherein converting the precursor MR imaging agent to the MR imaging agent comprises:

(a) reacting the precursor imaging agent with a precursor chelate moiety to form a covalent bond between the precursor chelate moiety and the linker moiety of the precursor MR imaging agent, the precursor chelate moiety comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties;

(b) transforming a plurality of the carboxylate precursor groups of the bound precursor chelate moiety to a plurality of carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and

(c) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to produce the MR imaging agent.

9. The method of claim 8, wherein the precursor chelate moiety is selected from the group consisting of:

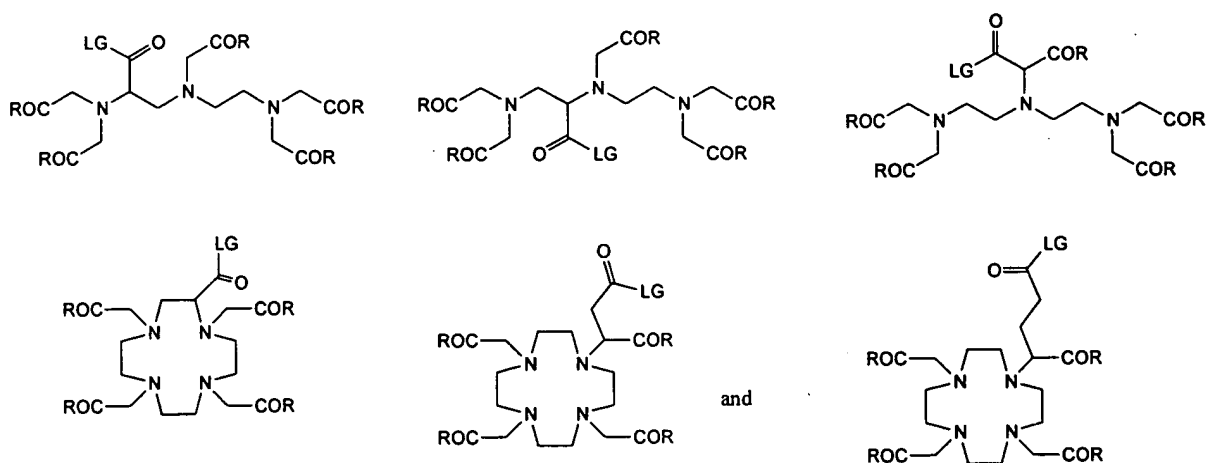


wherein Y is a synthetic moiety capable of forming a covalent bond with the attached linker moiety, and wherein each X, independently, is an  $O^-$  or an  $O^-$  precursor so that X, upon conversion to  $O^-$ , is capable of forming a carboxylate moiety with its adjacent carbonyl, and

$R^1$  is an uncharged chemical moiety, an aliphatic, alkyl group, or cycloalkyl group, or uncharged substituted versions thereof.

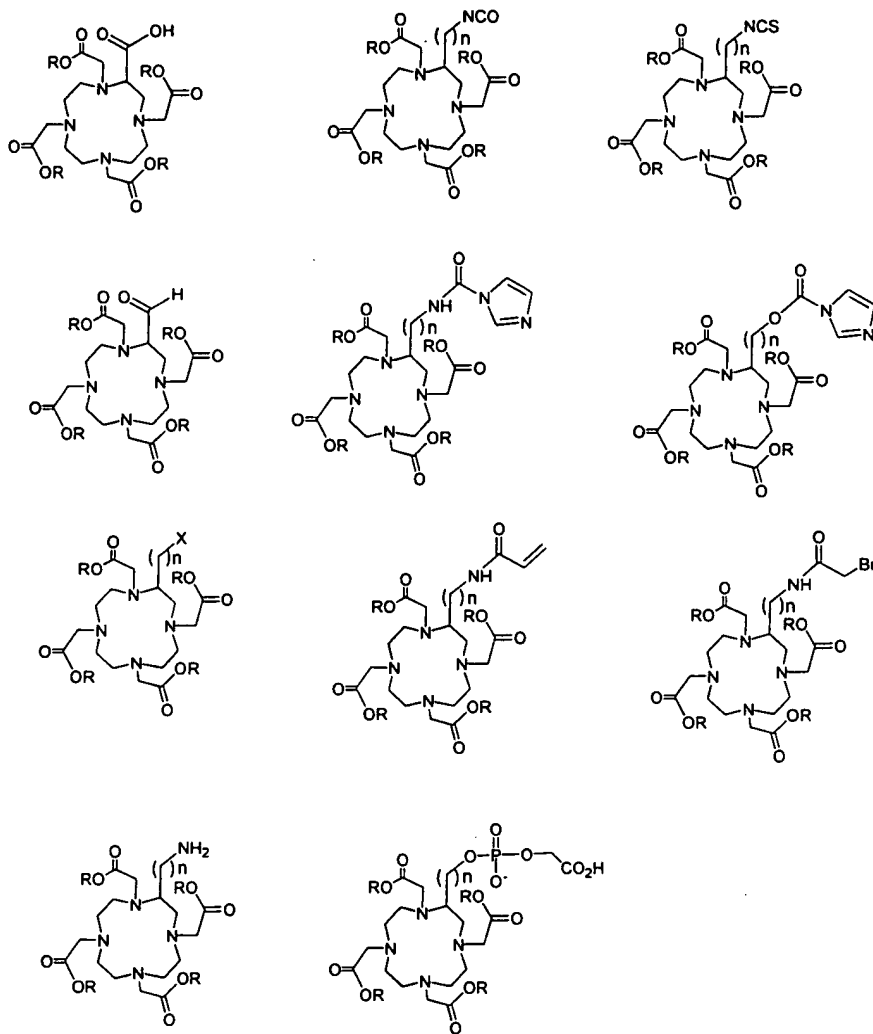
10. The method of claim 9, wherein the synthetic moiety is selected from the group consisting of a carboxylic acid, activated ester, acid halide, anhydride, alkyl halide, isocyanate, and isothiocyanate, and wherein the  $O^-$  precursor is selected from the group consisting of  $-OH$ ,  $-OMe$ ,  $OEt$ ,  $OtBu$ ,  $Obenzyl$ , and  $O$ -allyl.

11. The method of claim 8, wherein the precursor chelate moiety is selected from the group consisting of:



wherein LG is a leaving group selected from the group consisting of  $-OH$ , activated ester, halide, and anhydride, and wherein each R, independently, is an  $O^-$  or an  $O^-$  precursor selected from the group consisting of  $OH$ ,  $-O-Me$ ,  $O-Et$ ,  $O-tBu$ ,  $O-benzyl$ , and  $O$ -allyl, so that R, upon conversion to  $O^-$ , is capable of forming a carboxylate moiety with its adjacent carbonyl.

12. The method of claim 8, wherein the precursor chelate moiety is selected from the group consisting of:



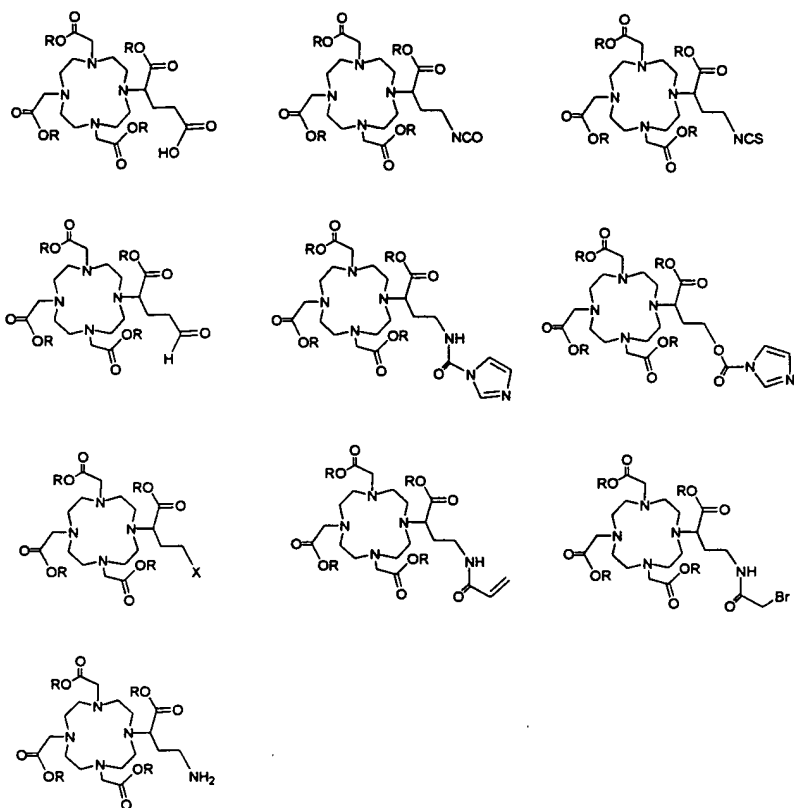
wherein:

$n$  is an integer from 1 to 4;

$R$  is selected from the group consisting of a negative charge and a negative charge precursor capable of being transformed into a negative charge; and

$X$  is a chemical leaving group selected from the group consisting of -Cl, -Br, -I, -MsO, -TsO, and -TfO.

13. The method of claim 8, wherein the precursor chelate moiety is selected from the group consisting of:



wherein:

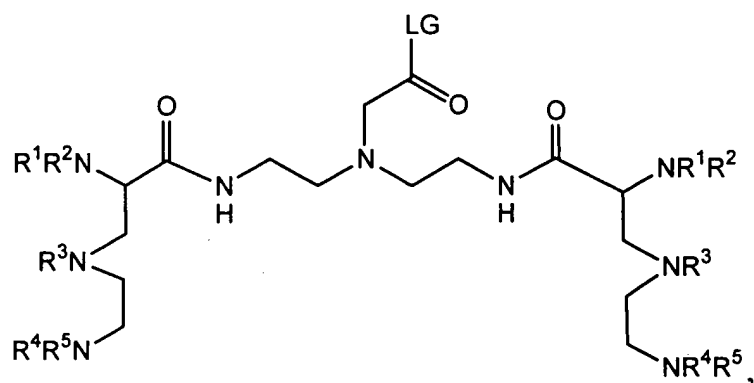
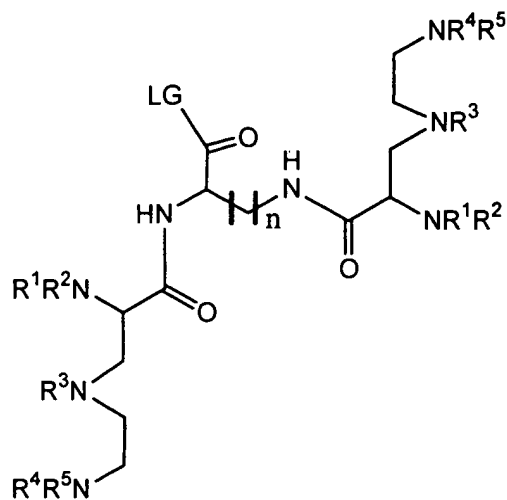
R is selected from the group consisting of a negative charge and a negative charge precursor capable of being transformed into a negative charge; and

X is a chemical leaving group selected from the group consisting of -Cl, -Br, -I, -MsO, -TsO, and -TfO.

14. The method of claim 12 or 13, wherein the negative charge precursor is selected from the group consisting of -H, -Me, -Et, -t-Bu, -benzyl, and -allyl.

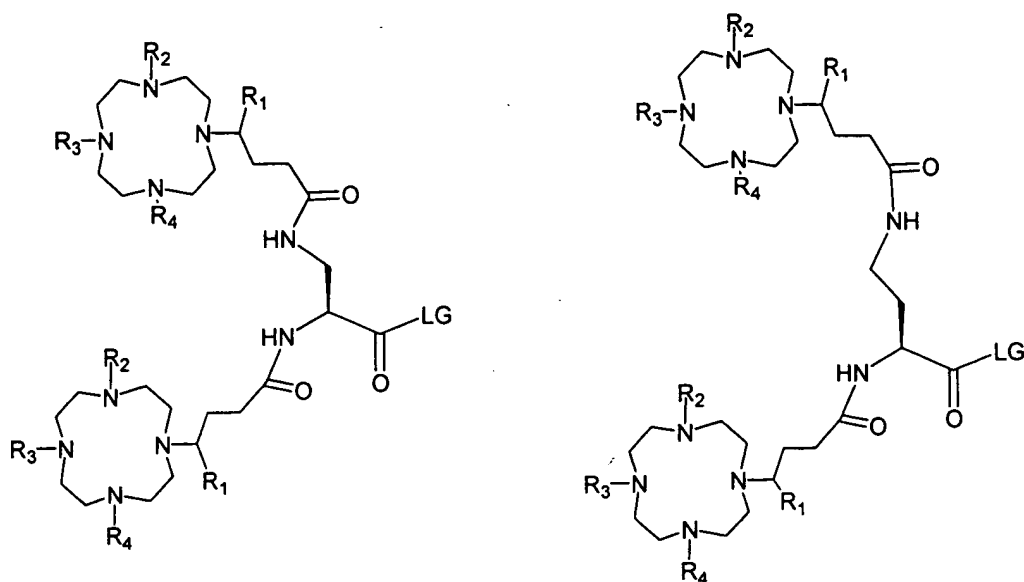
15. The method of claim 1, wherein the linker moiety is covalently conjugated to a precursor chelate moiety, the covalent conjugate comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties.

16. The method of claim 15, wherein the covalent conjugate is selected from the group consisting of



17. The method of claim 15, wherein the covalent conjugate is selected from the group consisting of:



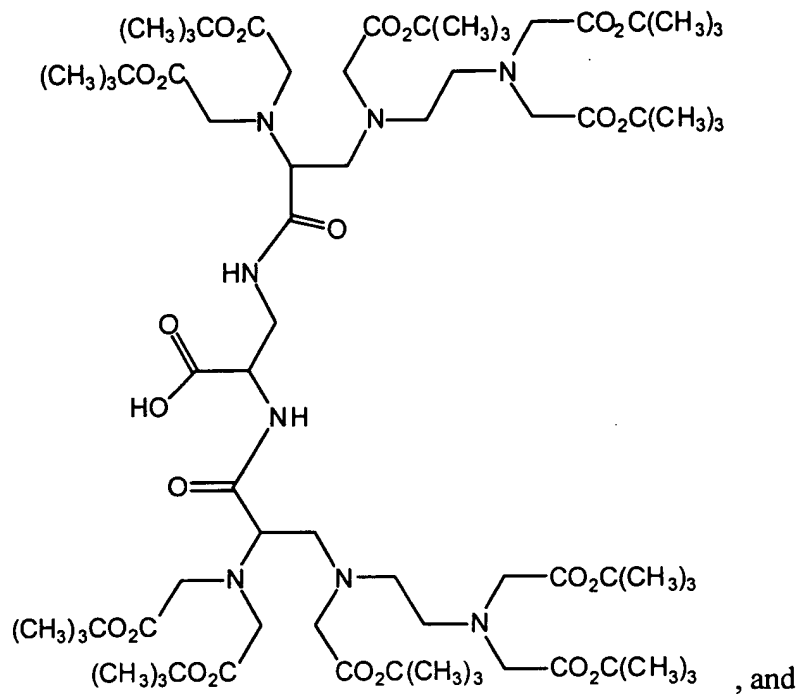
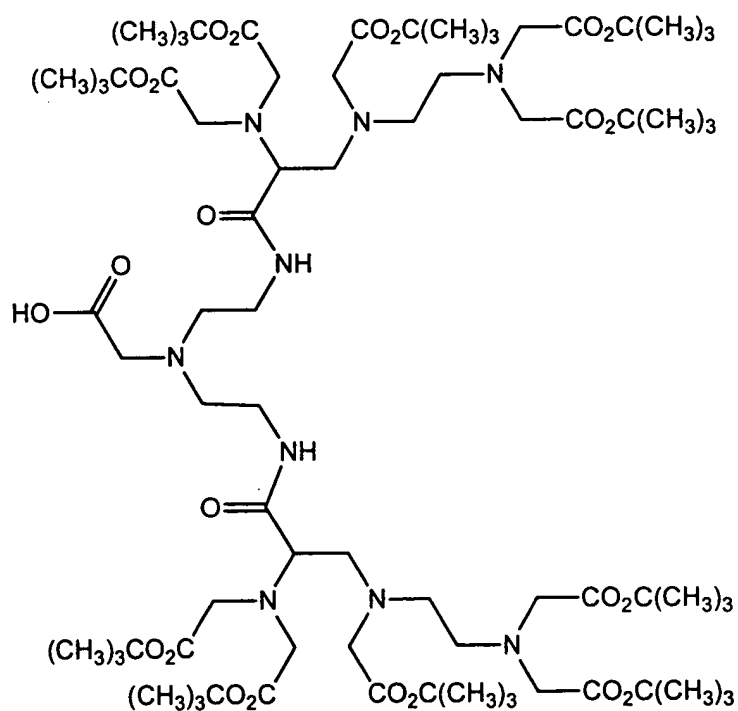


wherein:

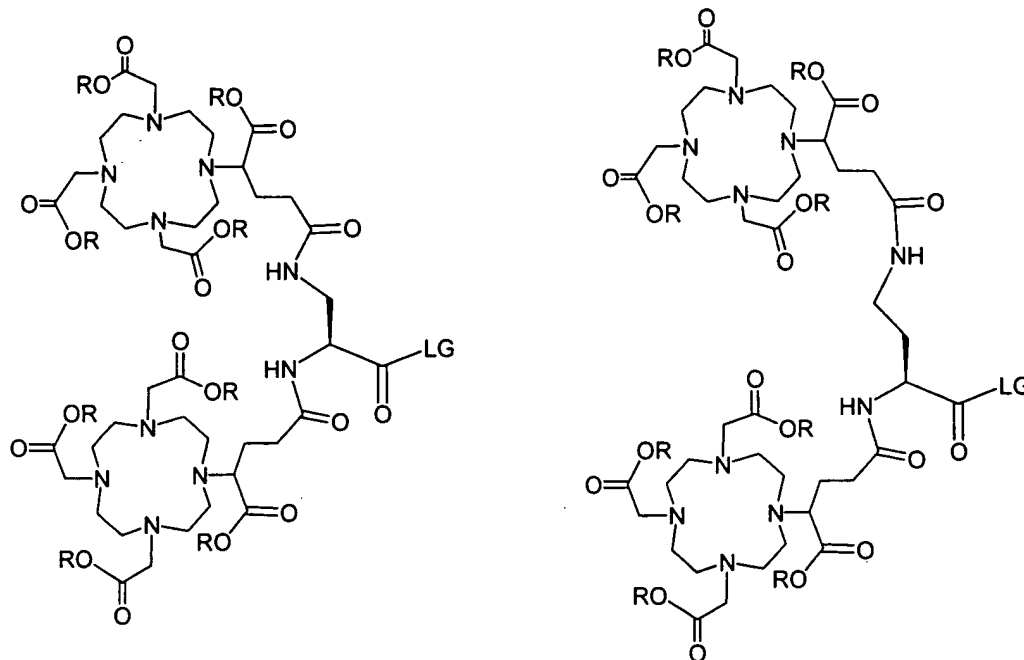
LG is a leaving group selected from the group consisting of  $-OH$ , activated ester, halide, and anhydride; and

$R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  are selected from the group consisting of an acetate moiety, a  $-Me$ ,  $-Et$ , or  $-t-Bu$  protected acetate moiety, an acetamide moiety, and an acetoxy moiety.

18. The method of claim 15, wherein the covalent conjugate is selected from the group consisting of:

**Synthon 1:****Synthon 2:**

19. The method of claim 15, wherein the covalent conjugate is selected from the group consisting of:



wherein:

R is a -tBu group,

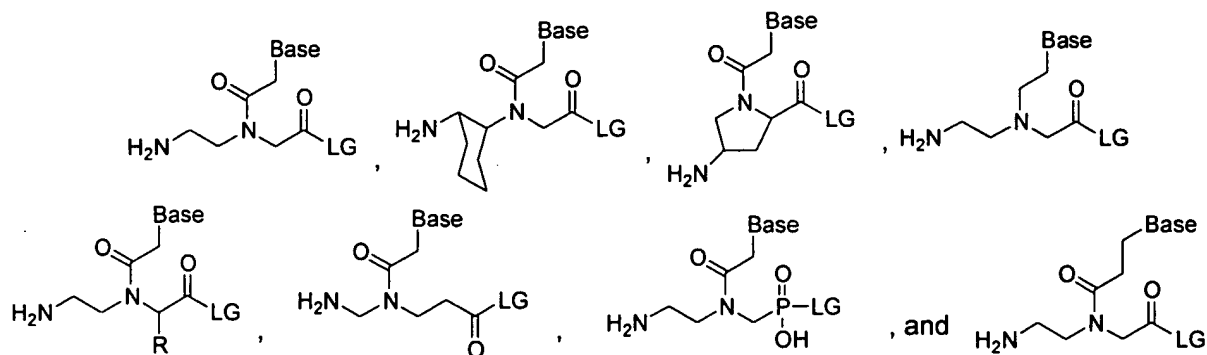
LG is a leaving group selected from the group consisting of -OH, activated ester, halide, and anhydride.

20. The method of claim 15, wherein converting the precursor MRI imaging agent to the MR imaging agent comprises:

- a) transforming a plurality of the covalent conjugate's carboxylate precursor groups into carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
- b) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to result in the MR imaging agent.

21. The method of claim 8 or claim 20, wherein the paramagnetic metal ion is selected from the group consisting of: Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III and IV), Ho(III), Er(III), Pr(III), Eu(II) and Eu(III).

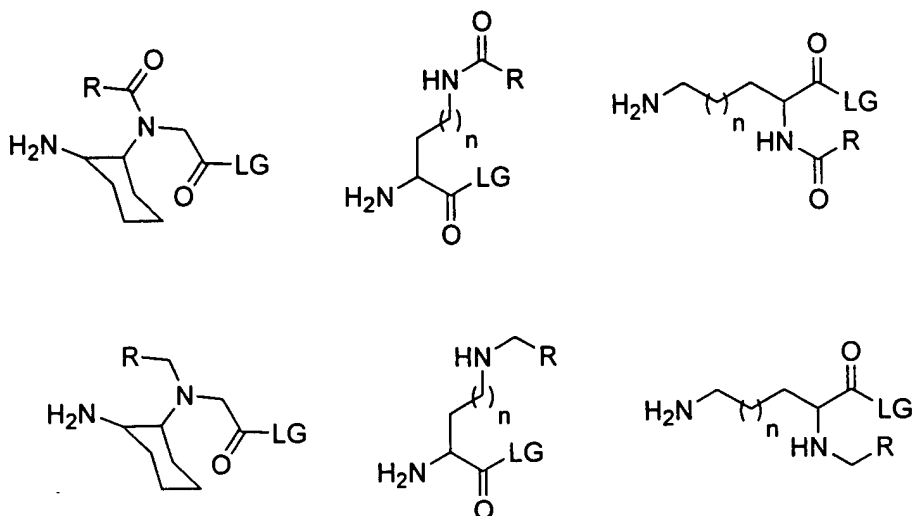
22. The method of claim 21, wherein the paramagnetic metal ion is Gd(III).
23. The method of claim 1, further comprising, prior to step b), reacting a linker-subunit with the N-terminal amine functional group of the peptide to result in a derivatized N-terminal amine functional group of the peptide.
24. The method of claim 23, wherein the linker-subunit is selected from the group consisting of:



wherein:

Base is selected from the group consisting of adenosine, guanosine, thymine, and cytosine;  
 LG is a leaving group selected from the group consisting of OH, activated ester, halide, and anhydride; and  
 R is an aliphatic or aromatic moiety.

25. The method of claim 23, wherein the linker-subunit is selected from the group consisting of:



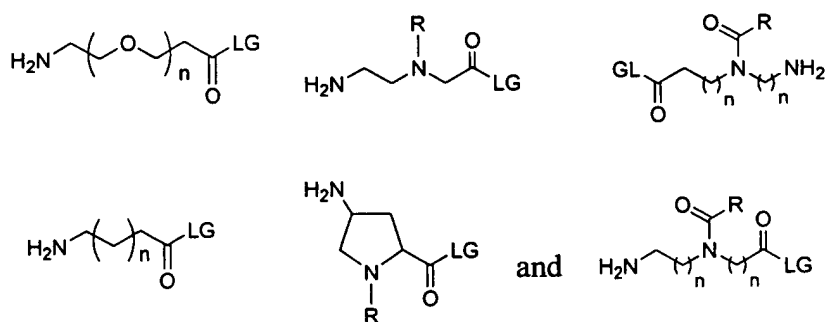
wherein:

$n$  is independently an integer from 0 to 3;

$R$  is an aliphatic or aromatic group; and

$LG$  is a leaving group selected from the group consisting of: OH, activated ester, halide, and anhydride.

26. The method of claim 23, wherein the linker-subunit is selected from the group consisting of:



wherein  $n$  is independently 1 or 2;

$R$  is an aliphatic or aromatic group; and

$LG$  is a leaving group selected from the group consisting of: OH, activated ester, halide, and anhydride.

27. A method of making a MR imaging agent, the method comprising:

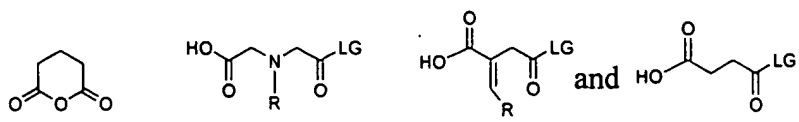
- a) covalently binding an amino acid residue to a linker-subunit moiety to form a C-terminal end of a peptide, wherein the linker-subunit moiety is covalently attached to a resin;
- b) synthesizing a peptide on the resin from the covalently bound C-terminal end to an N-terminal residue of the peptide, the N-terminal residue comprising an N-terminal amine functional group;
- c) cleaving the peptide from the resin to produce a peptide having a C-terminal amine functional group;
- d) covalently attaching a linker moiety to the peptide's C-terminal amine functional group and N-terminal amine functional group to form a precursor MR imaging agent; and
- e) converting the precursor MR imaging agent to the MR imaging agent.

28. The method of claim 27, wherein the method further comprises, prior to step c), covalently attaching a linker-subunit moiety to the N-terminal amino functional group to produce a derivatized N-terminal amine functional group.

29. The method of claim 27, wherein converting the precursor MR imaging agent to the MR imaging agent comprises:

- a) reacting the precursor MR imaging agent with a precursor chelate moiety to form a covalent bond between the precursor chelate moiety and the linker moiety of the precursor MR imaging agent, the precursor chelate moiety comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties;
- b) transforming a plurality of the carboxylate precursor groups of the bound precursor chelate moiety to a plurality of carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
- c) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to produce the MR imaging agent.

30. The method of claim 27, wherein the linker moiety is covalently conjugated to a precursor chelate moiety, the covalent conjugate comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties.
31. The method of claim 30, wherein converting the precursor MRI imaging agent to the MR imaging agent comprises:
- a) transforming a plurality of the covalent conjugate's carboxylate precursor groups into carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
  - b) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to result in the MR imaging agent.
32. The method of claim 31, wherein the paramagnetic metal ion is selected from the group consisting of: Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III and IV), Ho(III), Er(III), Pr(III), Eu(II) and Eu(III).
33. The method according to claim 31, wherein the paramagnetic metal ion is Gd(III).
34. A method of making a MR imaging agent, the method comprising:
- a) reacting a peptide having a C-terminal carboxylate functional group with a linker-subunit moiety to form a modified peptide having both a C-terminal carboxylate functional group and an N-terminal carboxylate functional group;
  - b) covalently attaching a linker moiety to both the N-terminal and C-terminal carboxylate functional groups of the modified peptide to form a precursor MR imaging agent; and
  - c) converting the precursor MR imaging agent to the MR imaging agent.
35. The method of claim 34, wherein the linker-subunit moiety is selected from the group consisting of:

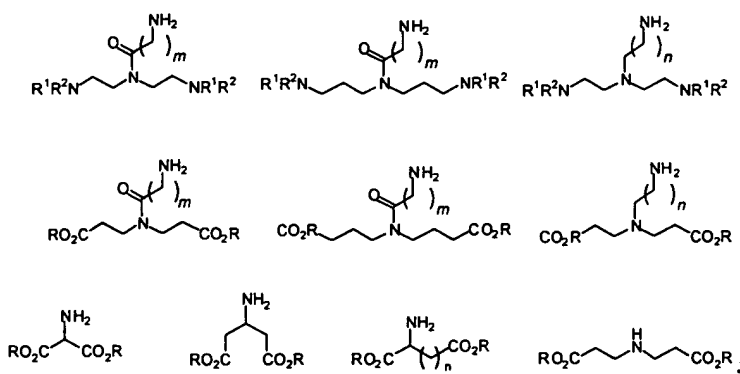


wherein;

LG is a leaving group selected from the group consisting of OH, activated ester, halide, and anhydride; and

R is an aromatic or aliphatic group.

36. The method of claim 34, wherein the linker moiety is selected from the group consisting of:



wherein:

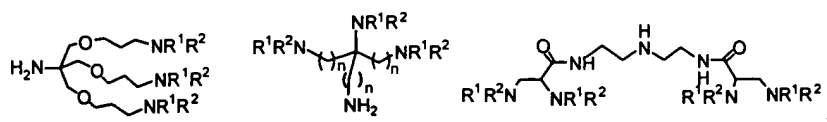
$m$  is an integer from 1 to 4;

n is an integer from 0 to 4;

R is independently selected from the group consisting of -H, -Me, -Et, -Bz, and -tBu; and

R<sup>1</sup> and R<sup>2</sup> are independently selected from a hydrogen or a chemical protecting group.

37. The method of claim 34, wherein the linker moiety is selected from the group consisting of:



wherein R<sup>1</sup> and R<sup>2</sup> are selected independently from the group consisting of hydrogen and a chemical protecting group, the chemical protecting group selected from the group consisting of: Boc, Fmoc, CBZ, t-butyl, benzyl, and allyl.



38. The method of claim 34, wherein converting the precursor MR imaging agent to the MR imaging agent comprises:

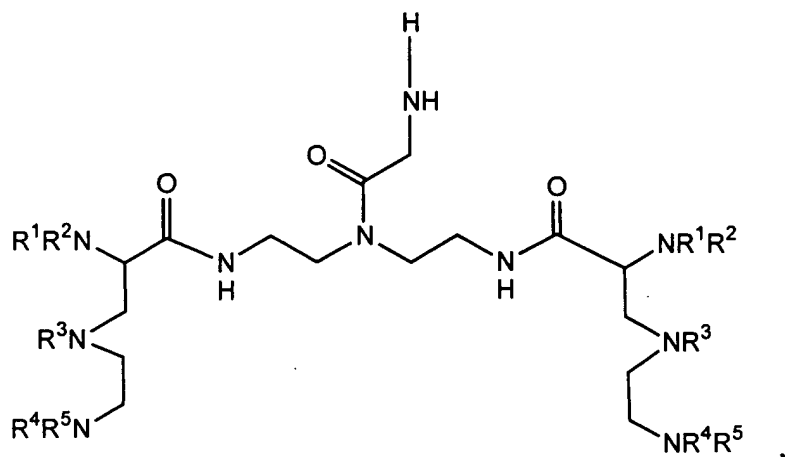
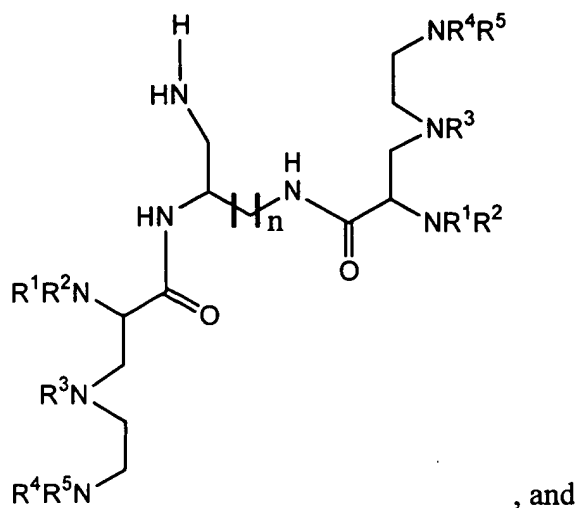
- a) reacting the precursor MR imaging agent with a precursor chelate moiety in order to form a covalent bond between the linker moiety of the precursor MR imaging agent and the precursor chelate moiety, the precursor chelate moiety comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties;
- b) transforming a plurality of the carboxylate precursor groups of the bound precursor chelate moiety to a plurality of carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
- c) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to produce the MR imaging agent.

39. The method of claim 34, wherein the linker moiety is covalently conjugated to a precursor chelate moiety, the covalent conjugate comprising a plurality of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties.

40. The method of claim 39, wherein converting the precursor MR imaging agent to the MR imaging agent comprises:

- a) transforming a plurality of the covalent conjugate's carboxylate precursor groups into carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
- b) complexing a paramagnetic metal ion to the plurality of carboxylate moieties to produce the MR imaging agent.

41. The method of claim 39, wherein the covalent conjugate is selected from the group consisting of:

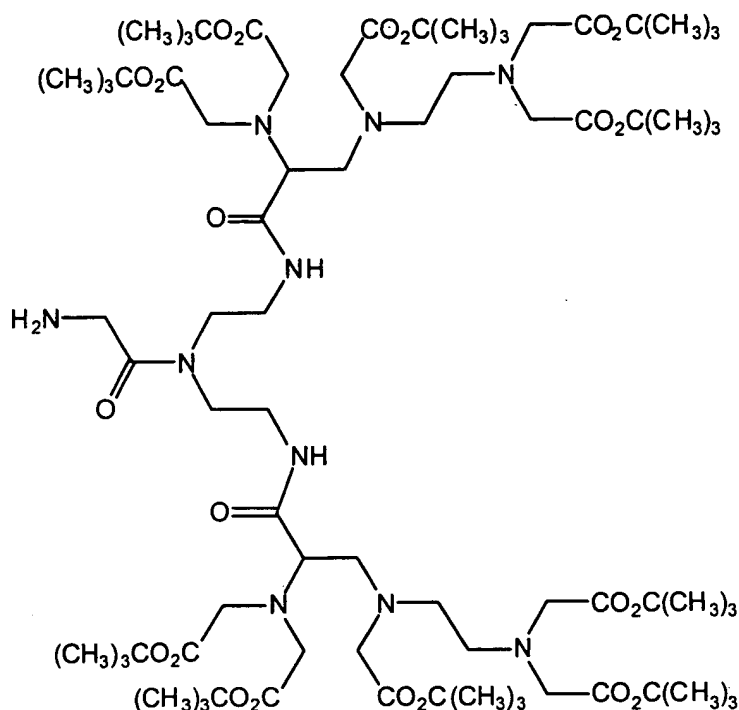


wherein:

$n$  is an integer from 1 to 4; and

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , and  $R^5$  are independently selected from the group consisting of an acetate moiety, a -Me, -Et, or -t-Bu protected acetate moiety, an acetamide moiety, and an acetoxy moiety.

42. The method of claim 39, wherein the covalent conjugate is:



43. A method of claim 1, claim 27, or claim 34, wherein converting the precursor MR imaging agent to the MR imaging agent comprises:

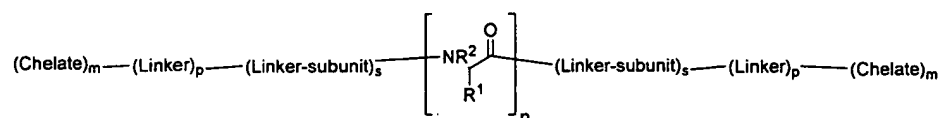
(a) reacting the precursor imaging agent with a chelate moiety, wherein the chelate moiety contains a paramagnetic metal ion, to form a covalent bond between the chelate moiety and the linker moiety of the precursor MR imaging agent to produce the MR imaging agent.

44. The method of claim 43, wherein the paramagnetic metal ion is selected from the group consisting of: Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III and IV), Ho(III), Er(III), Pr(III), Eu(II) and Eu(III).

45. The method of claim 44, wherein the paramagnetic metal ion is Gd(III).

46. A contrast agent comprising a metal chelate complex at a  $-\text{CO}_2\text{R}$  and  $\text{NHR}$  termini of a biopolymer, wherein R is independently selected from the group consisting of hydrogen, alkyl, aliphatic, and a leaving group.

47. The contrast agent of claim 46, comprising two metal chelate complexes at the CO<sub>2</sub>R and NHR termini of the biopolymer.
48. The contrast agent of claim 46, wherein the biopolymer has a specific binding affinity for fibrin.
49. The contrast agent of claim 46, wherein the biopolymer is a peptide.
50. The contrast agent of claim 49, wherein the peptide is capable of forming a disulfide bond under non-reducing conditions.
51. The contrast agent of claim 50, wherein the peptide comprises a disulfide bond.
52. The contrast agent of claim 46, the contrast agent having the formula:



wherein:

Chelate represents a metal chelate complex;

Linker represents a linker moiety;

Linker-subunit represents a linker-subunit moiety;

m is independently an integer from 1 to 10;

p is independently an integer from 0 to 5;

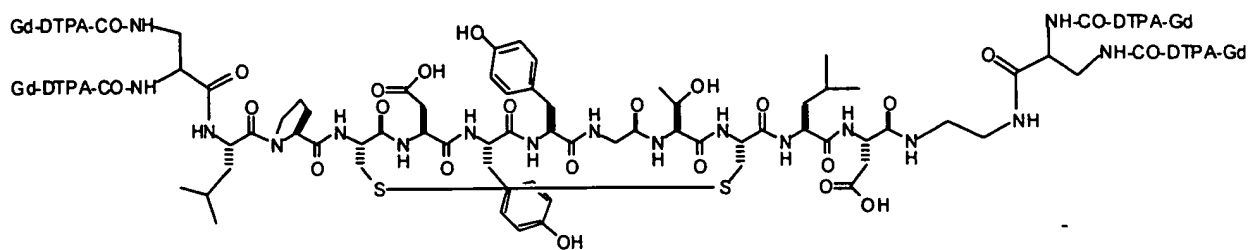
s is independently 0 or 1;

R<sup>1</sup> is an amino acid side chain or a derivative thereof; and

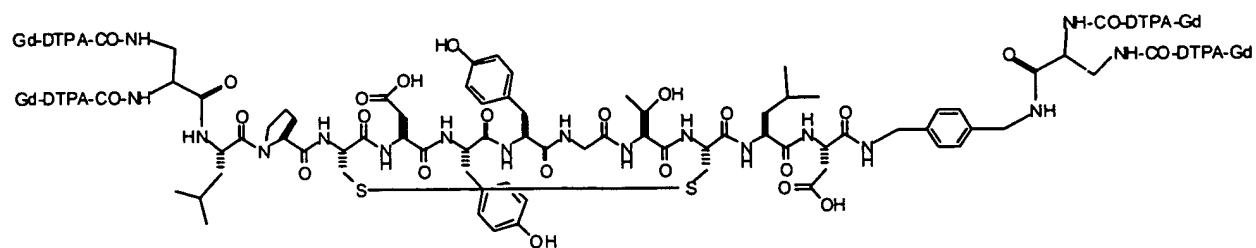
R<sup>2</sup> is independently a hydrogen or an aliphatic group.

53. The contrast agent of claim 52, the contrast agent having a structure selected from the group consisting of:

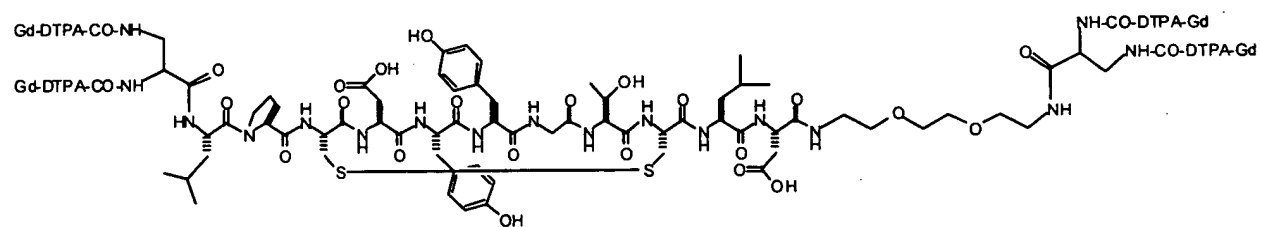
Structure 4



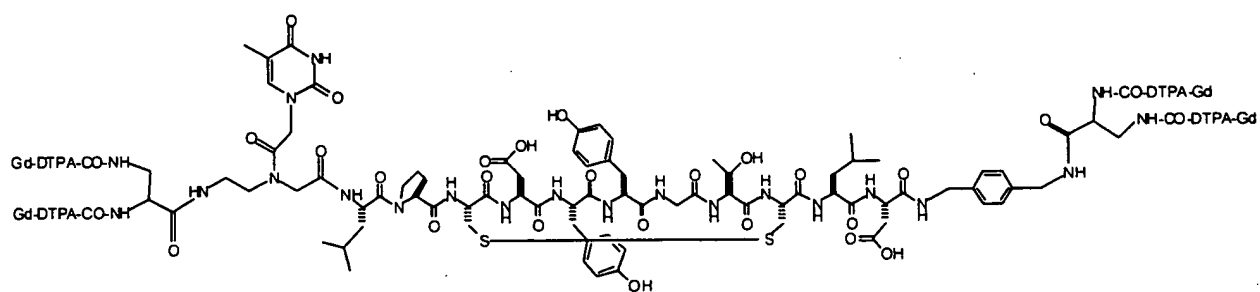
Structure 5



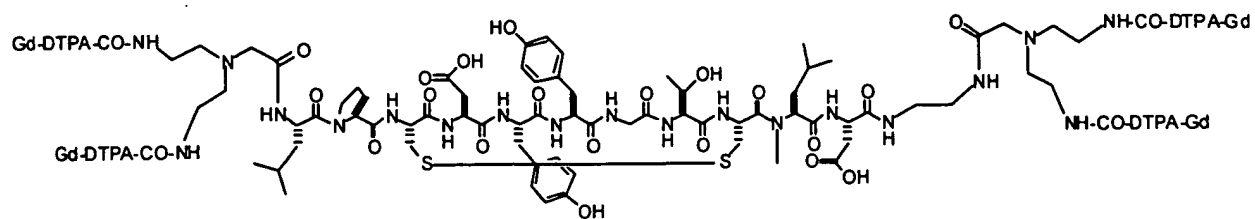
Structure 6



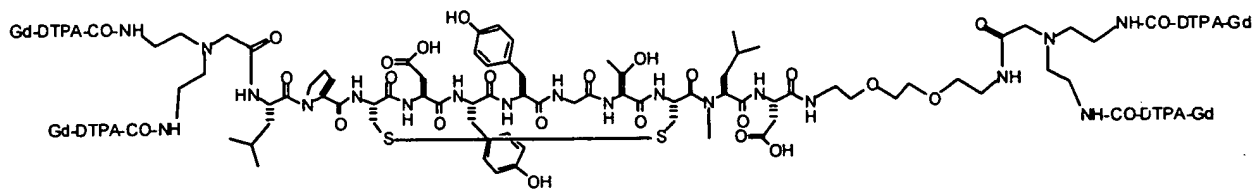
Structure 7



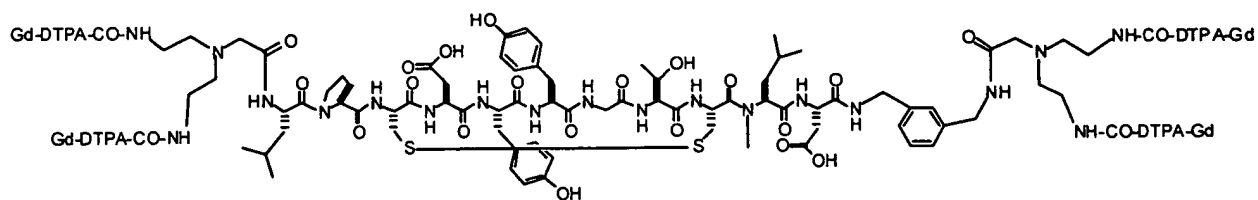
Structure 8



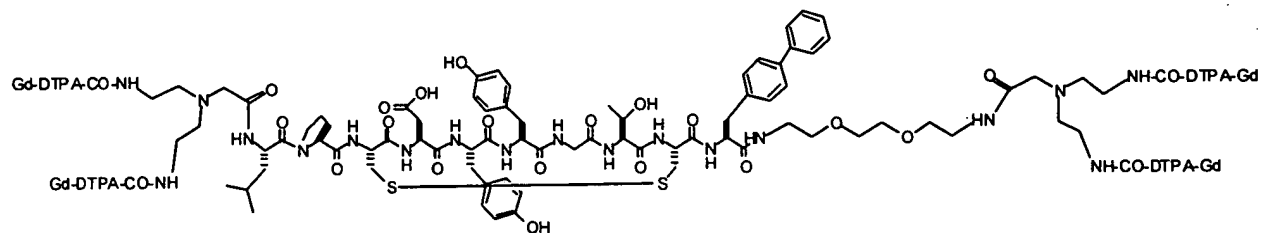
Structure 9



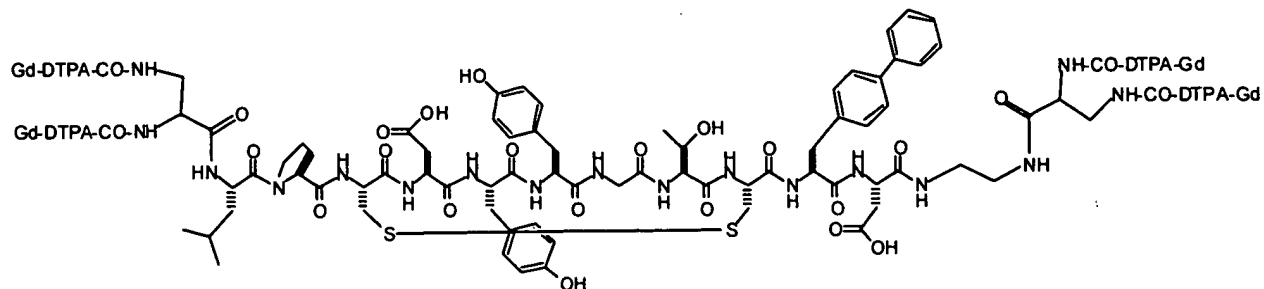
Structure 10



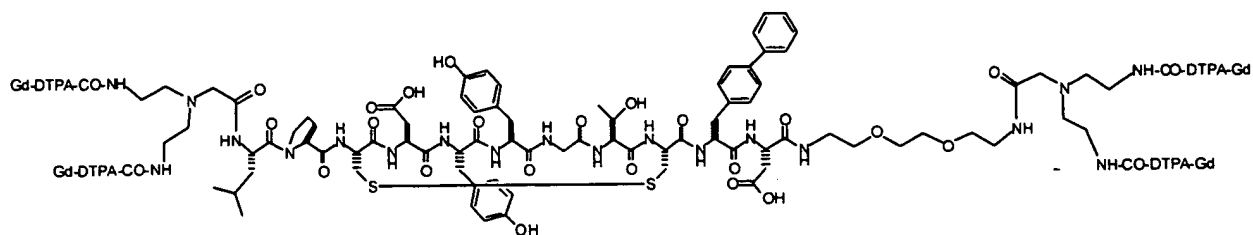
Structure 11



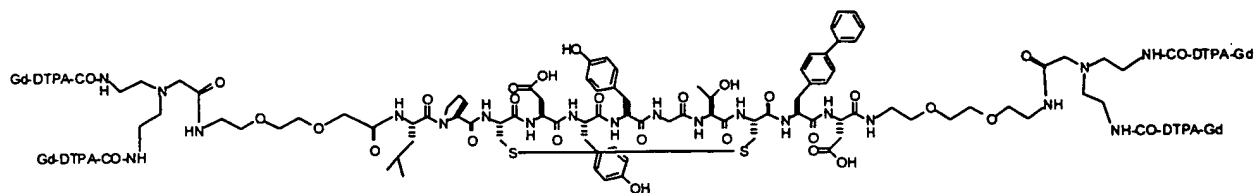
Structure 12



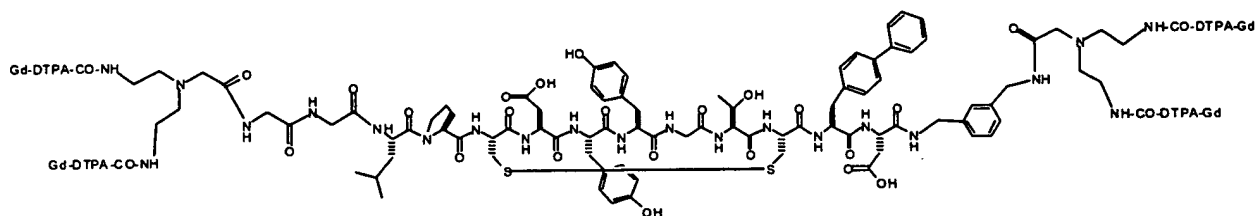
Structure 13



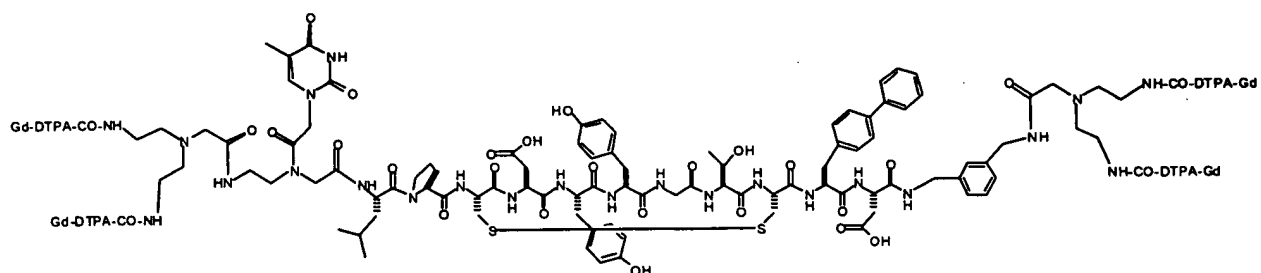
Structure 14

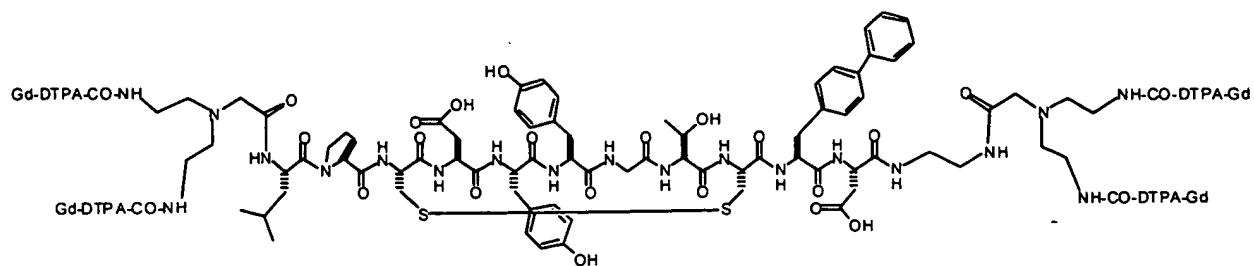
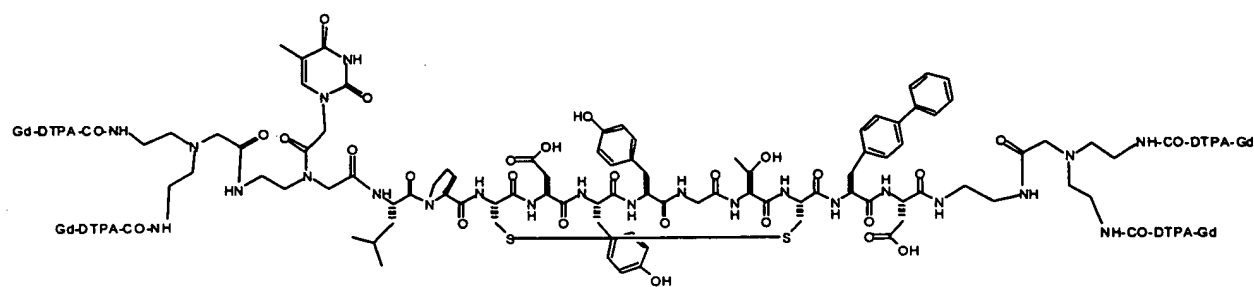
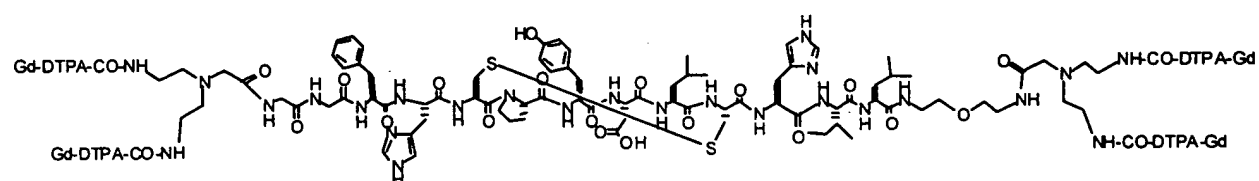
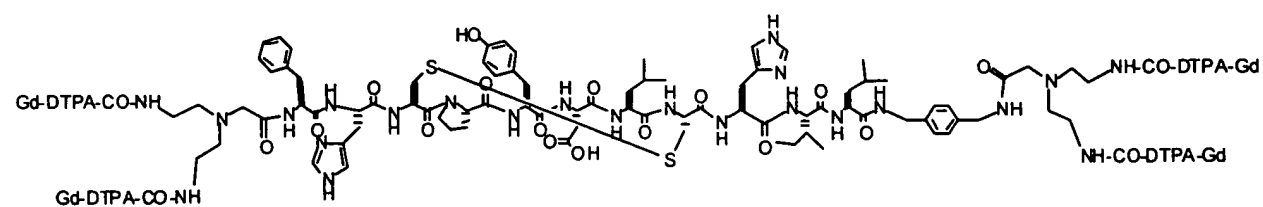


Structure 15



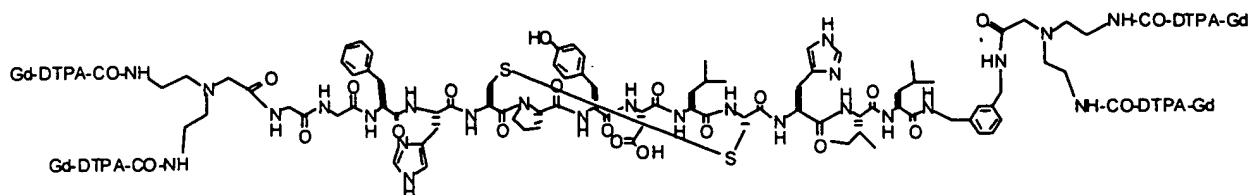
Structure 16



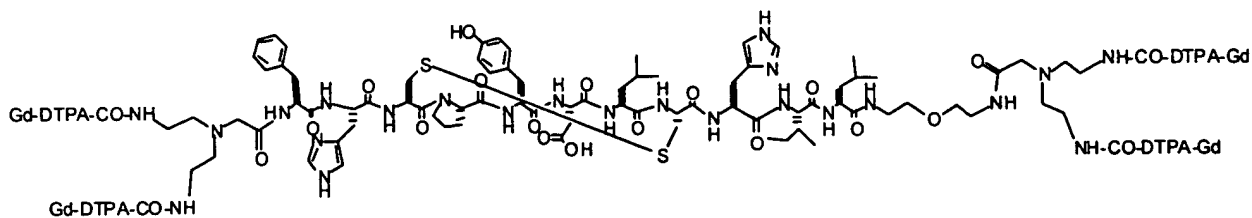
**Structure 17****Structure 18****Structure 19****Structure 20**



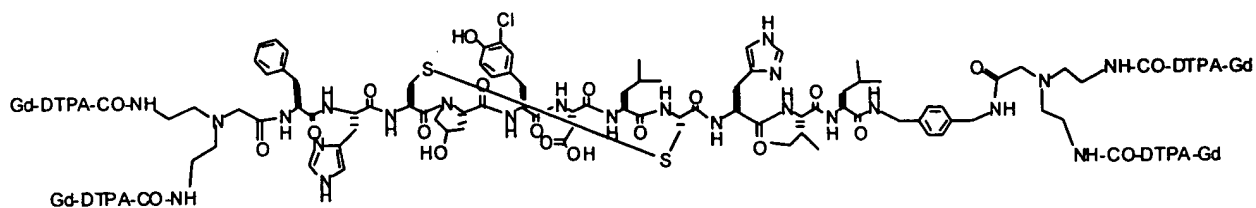
Structure 21



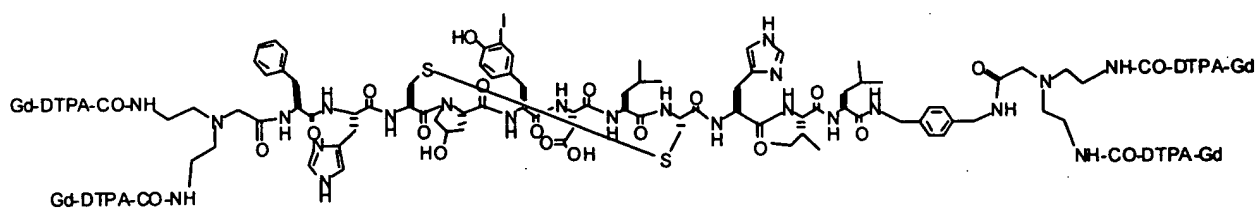
Structure 22



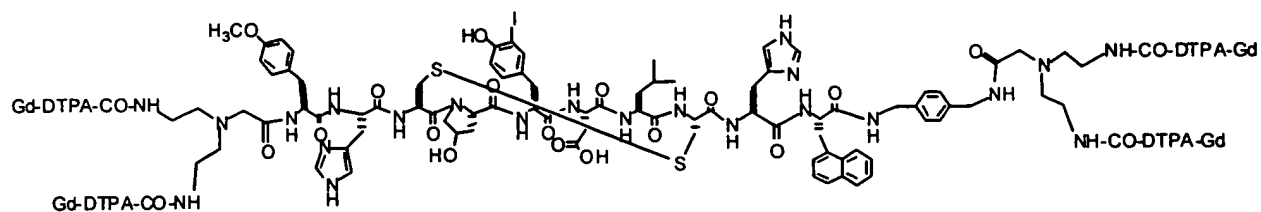
Structure 23



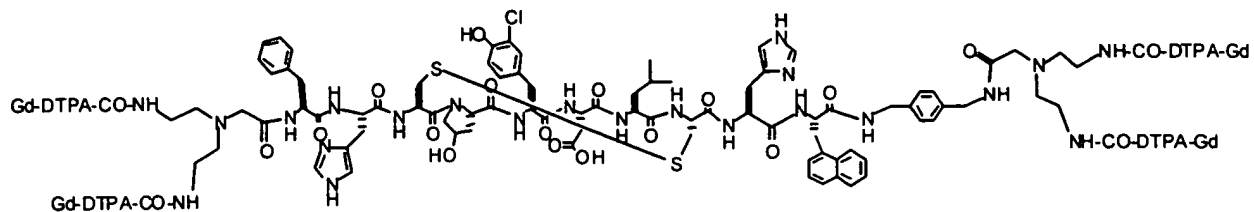
Structure 24



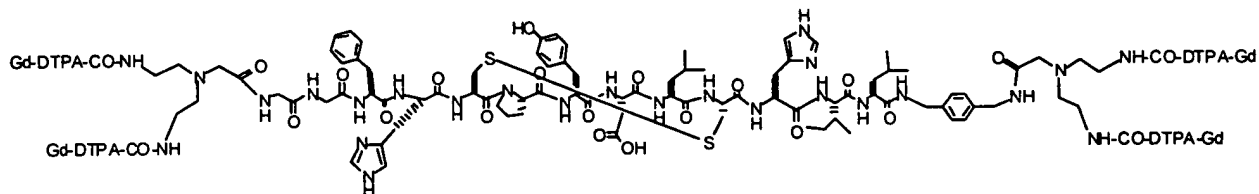
Structure 25



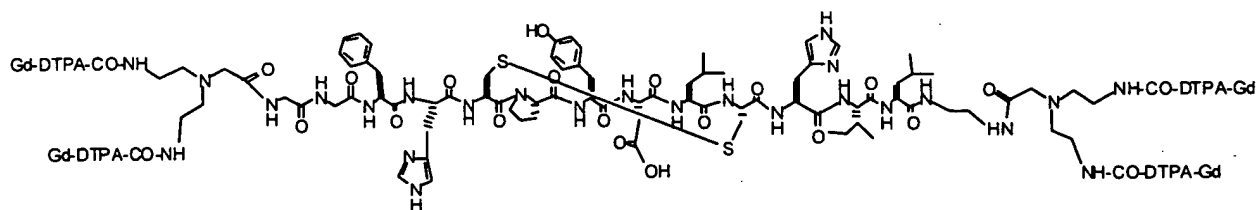
Structure 26



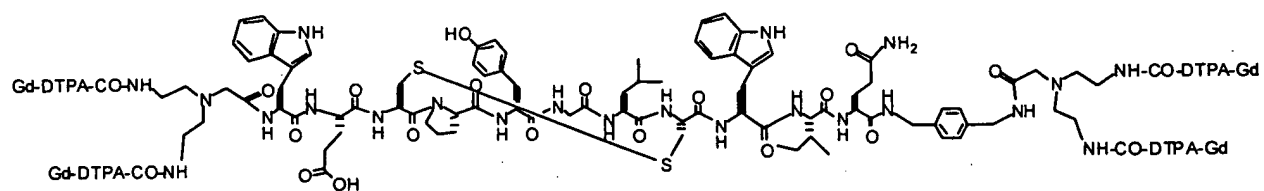
Structure 27



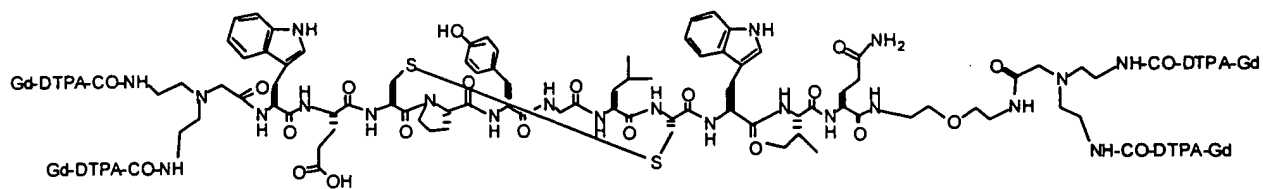
Structure 28

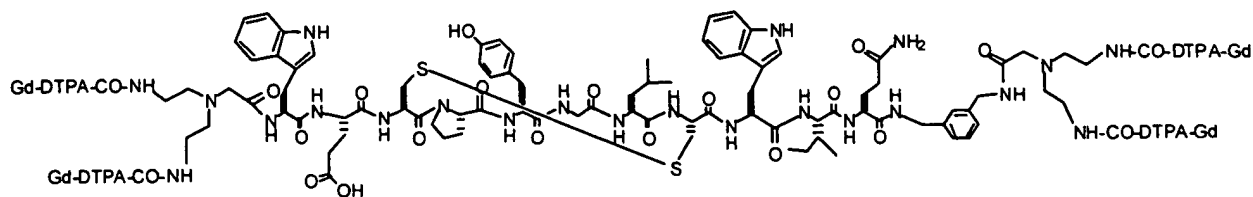


Structure 29

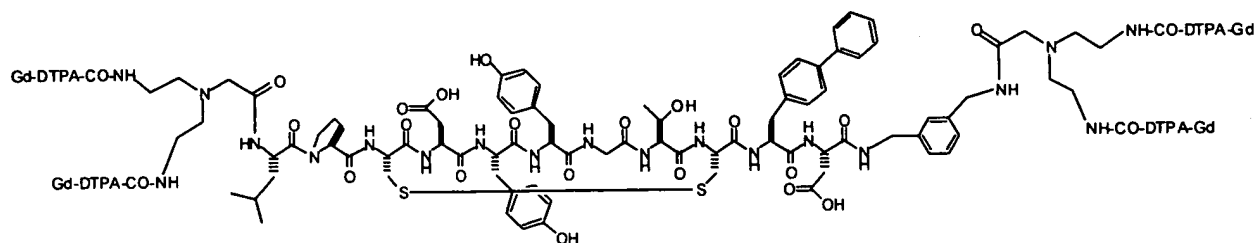


Structure 30



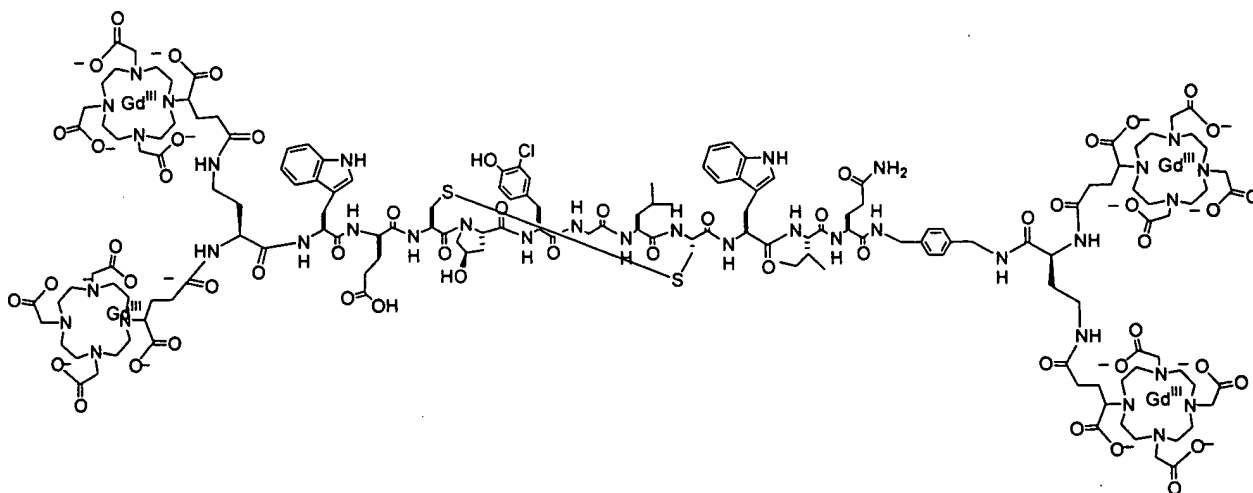
**Structure 31**

and

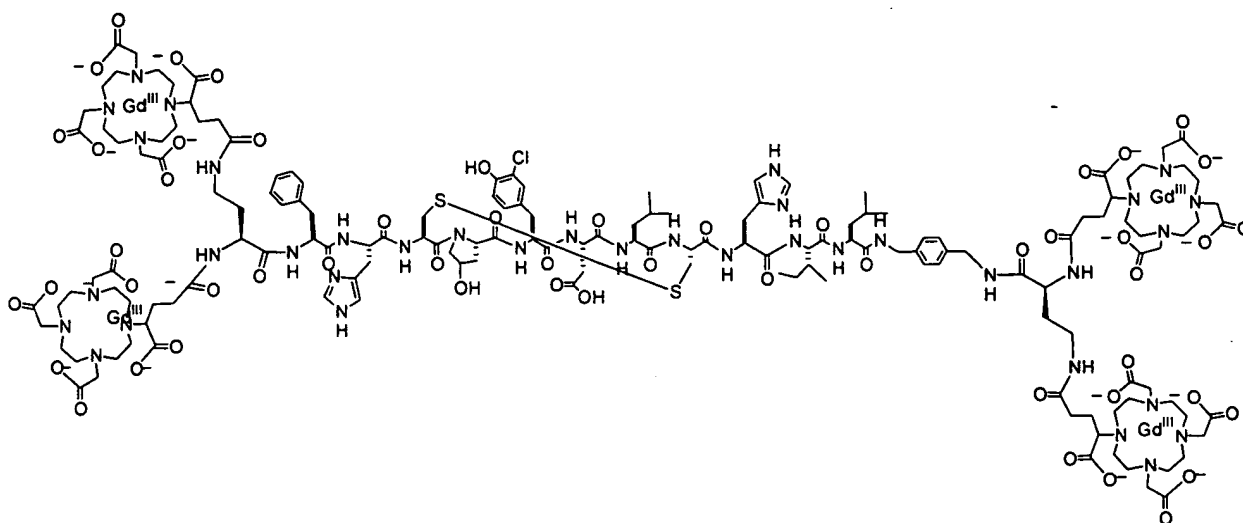
**Structure 32**

wherein Gd is a paramagnetic metal ion Gd(III), and wherein the Gd(III) is coordinated to the DTPA moiety; and wherein the DTPA moiety is covalently linked to a moiety comprising a C(=O) group at an ethylene or acetate carbon on the DTPA moiety.

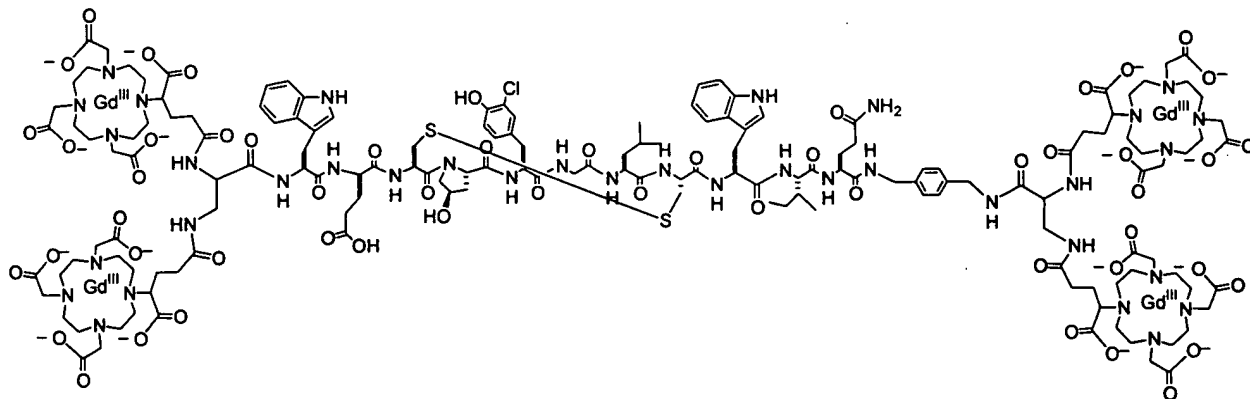
54. The contrast agent of claim 52, the contrast agent having a structure selected from the group consisting of:

**Structure 33**

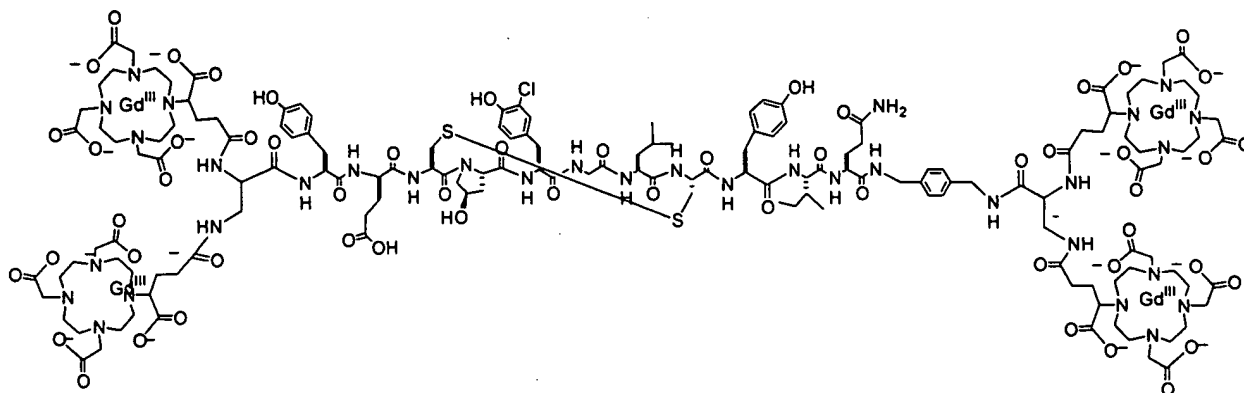
Structure 34



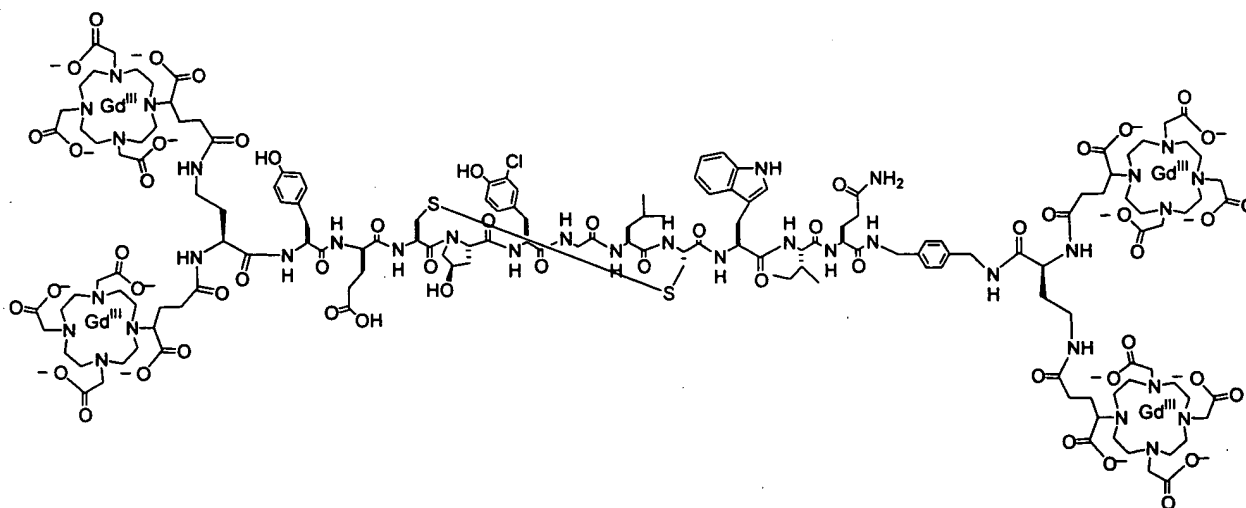
Structure 35



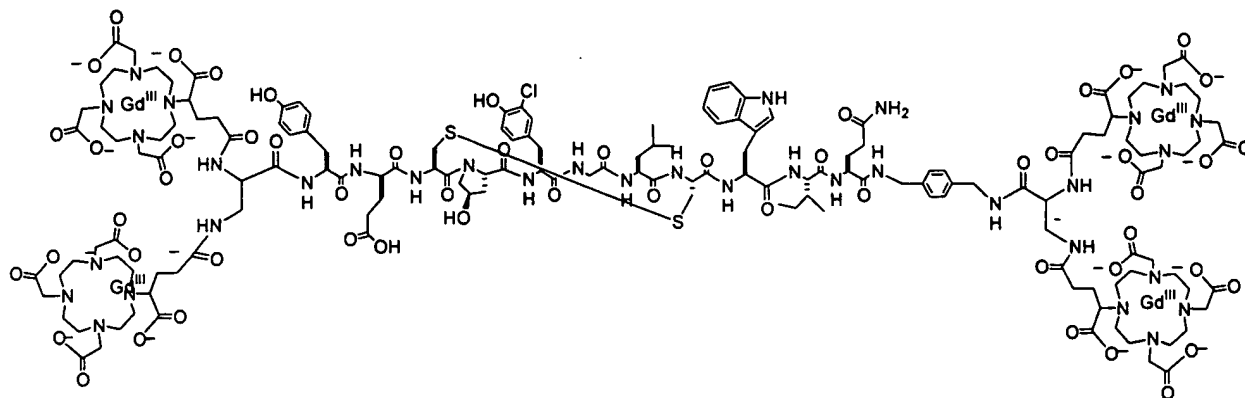
Structure 36



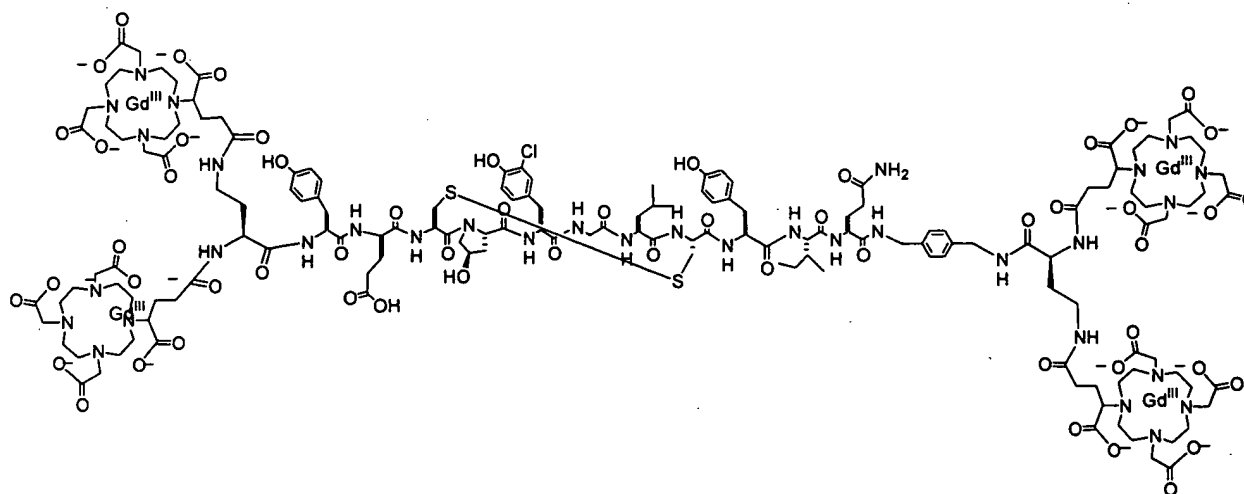
Structure 37

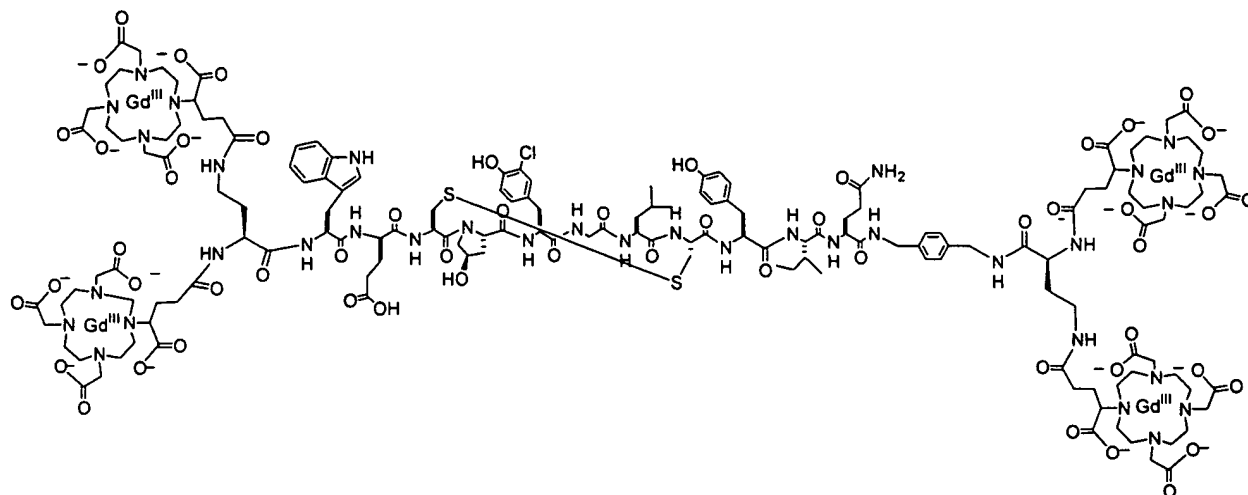


Structure 38

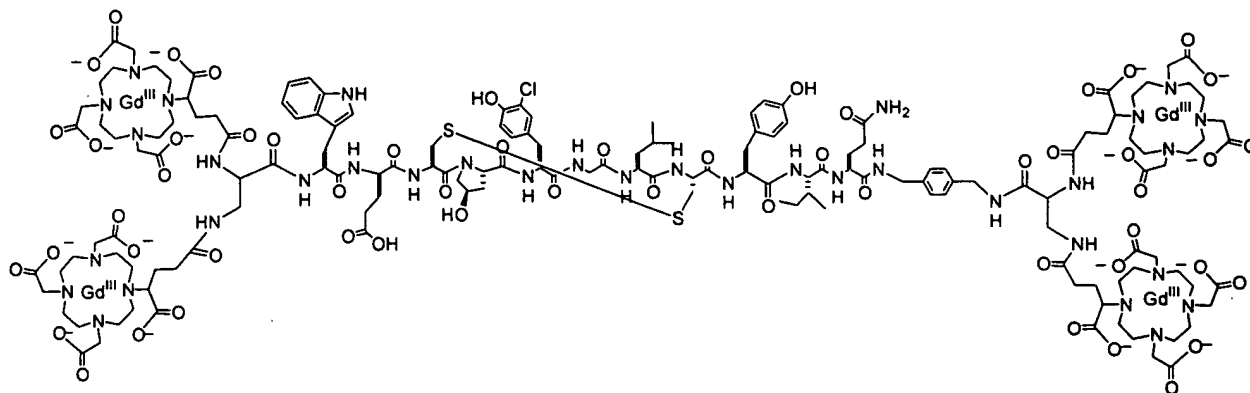


Structure 39



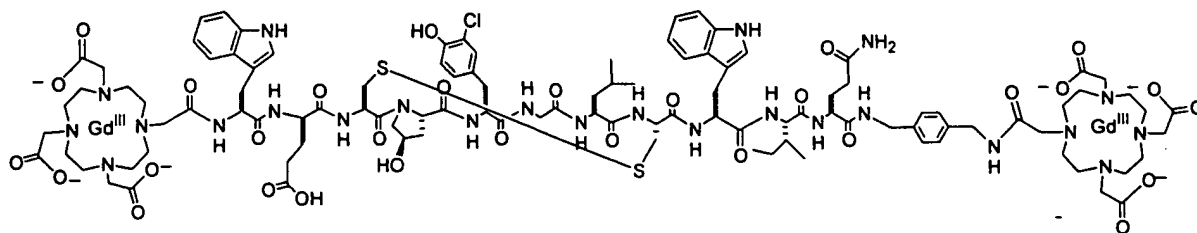
**Structure 40**

and

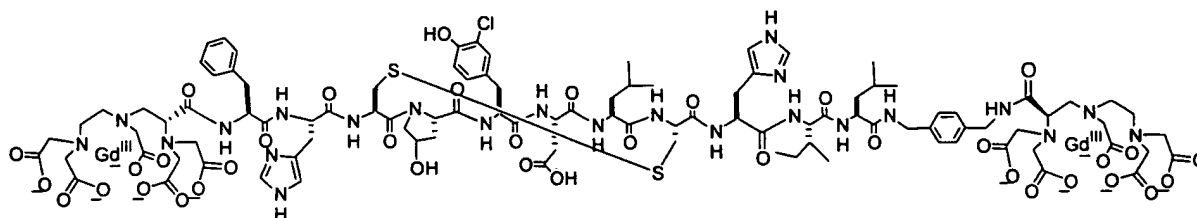
**Structure 41**

55. The contrast agent of claim 52, the contrast agent having a structure selected from the group consisting of:

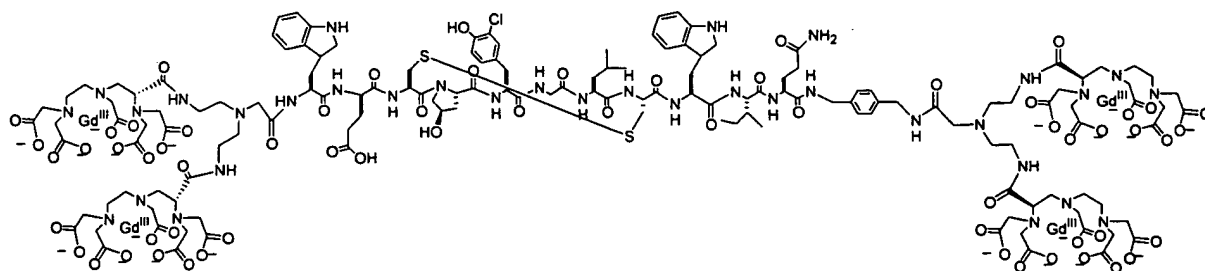
Structure 42



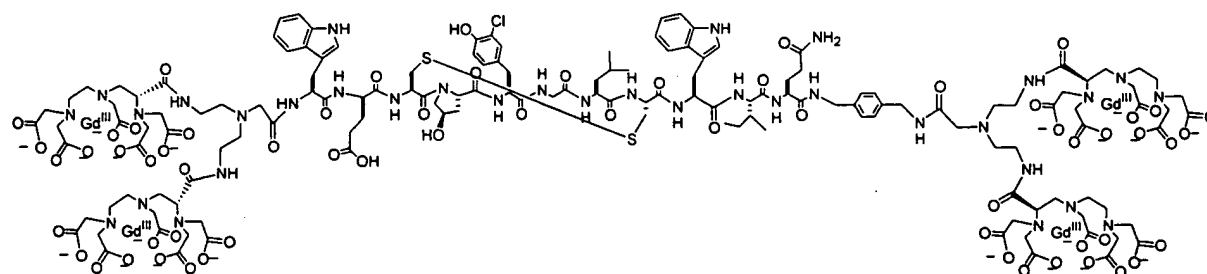
Structure 43



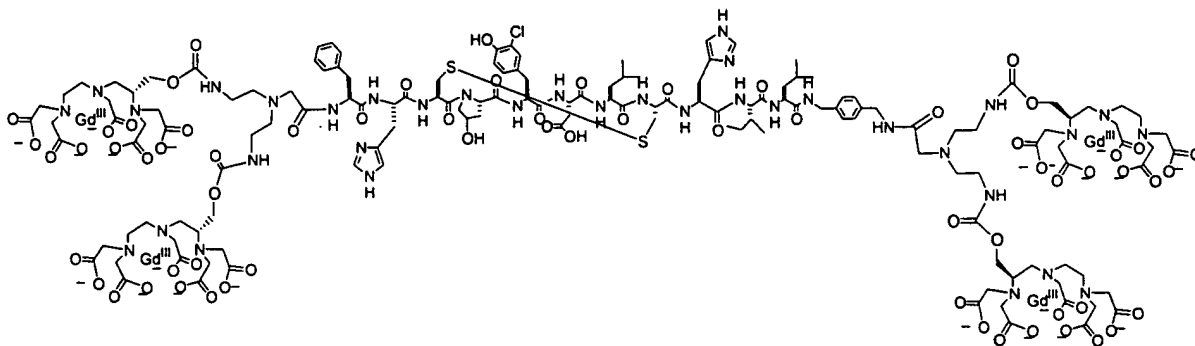
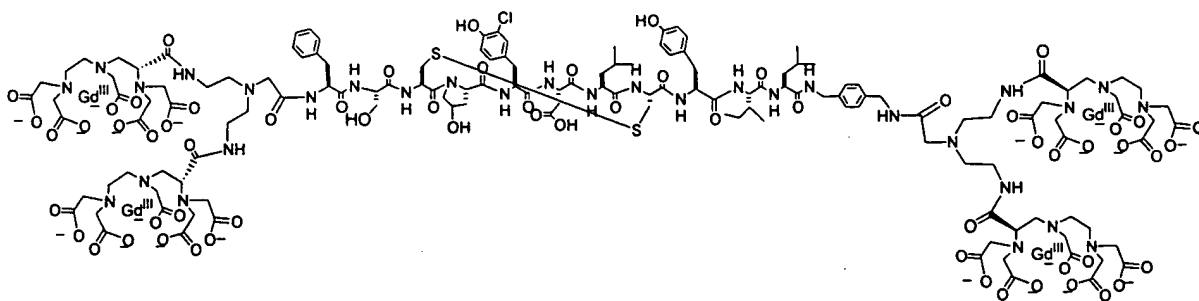
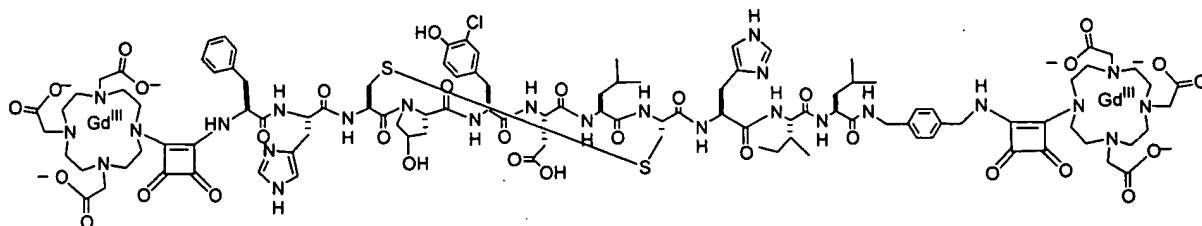
Structure 44

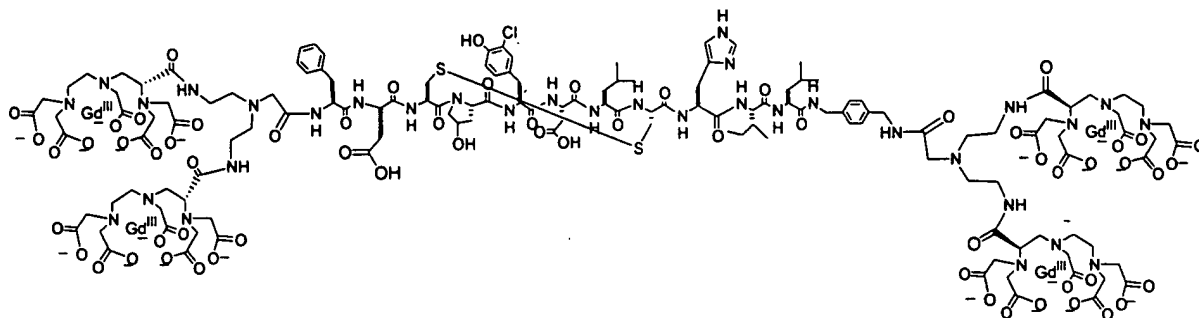


Structure 45

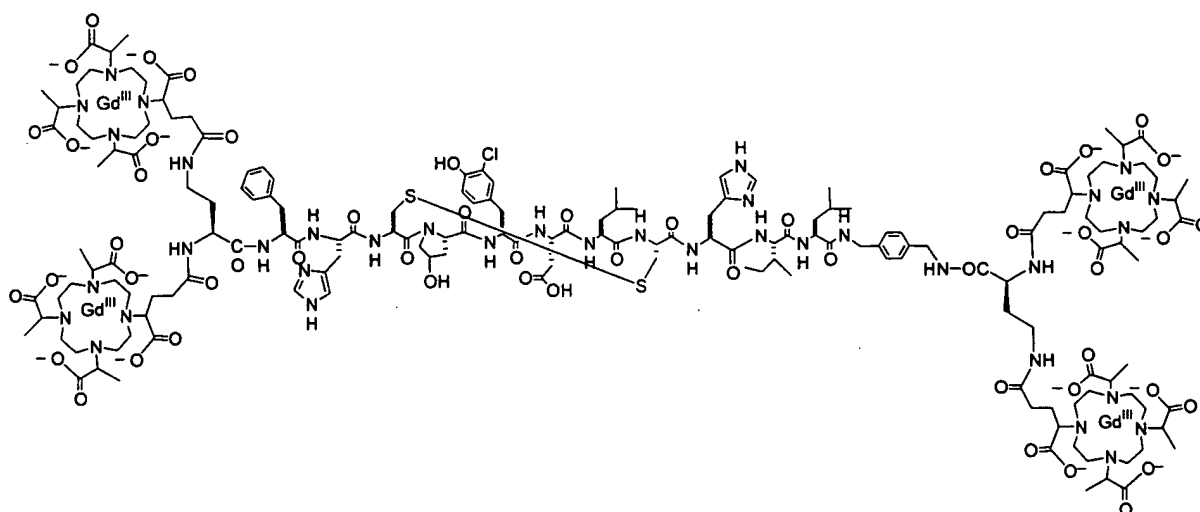




**Structure 46****Structure 47****Structure 48**

**Structure 49**

and

**Structure 50**

56. A method for altering the stability of a peptide, the peptide having an N-terminal amine functional group, the method comprising:

- a) reacting the peptide with a linker-subunit moiety to form a peptide having a C-terminal amine functional group; and
- b) covalently attaching a linker moiety to the peptide's C-terminal amine functional group and N-terminal amine functional group to form a modified peptide.

57. The method of claim 56, further comprising reacting the modified peptide with a precursor chelate moiety to form a covalent bond between the precursor chelate moiety and the linker moiety of the modified peptide, the precursor chelate moiety comprising a plurality

of carboxylate precursor groups, the carboxylate precursor groups capable of being transformed into carboxylate moieties.

58. The method of claim 57, further comprising:

- (a) transforming a plurality of the carboxylate precursor groups of the bound precursor chelate moiety to a plurality of carboxylate moieties, the carboxylate moieties capable of complexing a paramagnetic metal ion; and
- (b) complexing a paramagnetic metal ion to the plurality of carboxylate moieties.

59. The method of claim 57, further comprising assaying the stability of the modified peptide.

60. The method of claim 57, further comprising:

- a) assaying the stability of said unmodified peptide; and
- b) comparing the stability of said modified peptide to the stability of said unmodified peptide.

61. The method of claim 60, wherein the stability of the modified peptide is improved relative to the stability of the unmodified peptide.

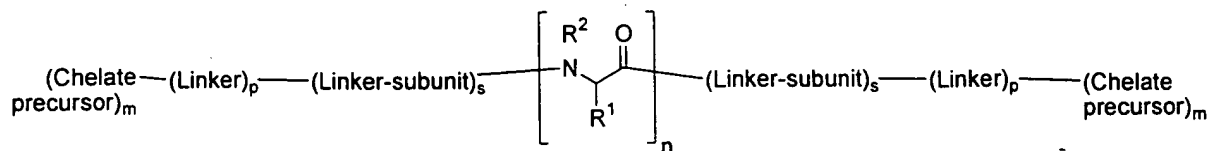
62. The method of claim 61, wherein the stability of the modified peptide is improved 10-fold relative to the stability of the unmodified peptide.

63. The method of claim 61, wherein the stability of the modified peptide is improved 20-fold relative to the stability of the unmodified peptide.

64. The method of claim 61, wherein the stability of the modified peptide is improved 30-fold relative to the stability of the unmodified peptide.

65. The method of claim 59 or claim 60, wherein the stability is assayed using a rat liver homogenate assay.

66. A modified peptide having the structure:



wherein:

Chelate precursor represents a chelate precursor moiety;

Linker represents a linker moiety;

Linker-subunit represents a linker-subunit moiety;

m is independently an integer from 1 to 10;

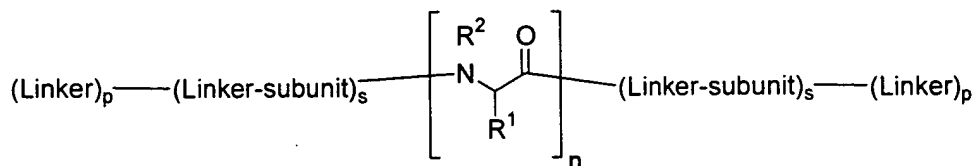
p is independently an integer from 0 to 5;

s is independently 0 or 1;

R<sup>1</sup> is an amino acid side chain or a derivative thereof; and

R<sup>2</sup> is selected from the group consisting of H and an aliphatic group.

67. A modified peptide having the structure:



wherein:

Linker represents a linker moiety;

Linker-subunit represents a linker-subunit moiety;

p is independently an integer from 0 to 5;

s is independently 0 or 1;

R<sup>1</sup> is an amino acid side chain or a derivative thereof; and

R<sup>2</sup> is selected from the group consisting of H and an aliphatic group.

68. A method of making an MR imaging agent, the method comprising:

- a) reacting a peptide having an N-terminal amine functional group with a linker-subunit moiety to form a modified peptide having an amine functional group on both its N-terminus and C-terminus; and
  - b) converting the modified peptide to the MR imaging agent.
69. A method of making an MR imaging agent, said method comprising:
- a) reacting a peptide having a C-terminal carboxylate functional group with a linker-subunit moiety to form a modified peptide having a carboxylate functional group on both its C-terminus and N-terminus; and
  - b) converting the modified peptide to the MR imaging agent.
70. A method of making an MR imaging agent, said method comprising:
- a) covalently binding an amino acid residue to a linker-subunit moiety to form a C-terminal end of a peptide, wherein the linker-subunit moiety is covalently attached to a resin;
  - b) synthesizing a peptide on the resin from the covalently bound C-terminal end to an N-terminal residue of the peptide, the N-terminal residue comprising an N-terminal amine functional group;
  - c) cleaving the peptide from the resin to produce a C-terminal amine functional group of the modified peptide;
  - d) converting the modified peptide to the MR imaging agent.
71. The method of claim 68, claim 69, or claim 70, wherein converting the modified peptide to the MR imaging agent comprises covalently attaching a chelate moiety to the modified peptide, wherein the chelate moiety contains a paramagnetic metal ion, to produce the MR imaging agent.
72. The method of claim 71, wherein the paramagnetic metal ion is selected from the group consisting of: Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III and IV), Ho(III), Er(III), Pr(III), Eu(II) and Eu(III).

73. The method of claim 71, wherein the paramagnetic metal ion is Gd(III).
74. The method of claim 68, claim 69, or claim 70, wherein converting the modified peptide to the MR imaging agent comprises:
- 5       a) covalently linking a linker moiety to a chelate moiety to form a covalent conjugate, wherein the chelate moiety contains a paramagnetic metal ion; and
- b) reacting the covalent conjugate with the modified peptide to form the MR imaging agent.
75. The method of claim 74, wherein the paramagnetic metal ion is selected from the group consisting of: Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III and IV),
- 10   Ho(III), Er(III), Pr(III), Eu(II) and Eu(III).
76. The method of claim 74, wherein the paramagnetic metal ion is Gd(III).
77. The method of claim 56, further comprising reacting the modified peptide with a
- 15   capping moiety to form a covalent bond between the capping moiety and the linker moiety of the modified peptide.